THE ROLE OF THE INFECTIOUS DISEASES PHYSICIAN IN SETTING GUIDELINES FOR ANTIMICROBIAL USE*

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THE plethora of potent new antimicrobial agents and the national mandate for cost control force us to rethink traditional guidelines for antimicrobial use. New compounds offer the potential for unprecedented efficacy and safety, but are nearly always more costly than older agents. Reimbursement by prospective payment changes the position of the hospital pharmacy from that of a revenue-generating center to that of a cost center. What constitutes optimal cost-effective antimicrobial therapy becomes increasingly difficult to determine, making ever more urgent the need for effective yet flexible guidelines for antimicrobial use.

How and by whom such guidelines should be established and implemented remain unclear. The dynamic changing nature of cost-effectiveness issues makes the periodic recommendations of textbooks and national comittees no longer sufficient for all settings. Each hospital must address this problem. At the most recent conference in this series, it was argued that "the infectious disease specialist is better trained in appropriate antimicrobial use" than other people, and would therefore be the logical member of the medical staff to formulate such guidelines.[1] I shall not review the ways by which infectious diseases specialists can influence their peers.[1,2] Instead, I shall review the general nature of the infectious diseases physician's involvement, beginning with the need to define more clearly what we mean by the phrase "appropriate antimicrobial therapy".

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What is "Appropriate Antimicrobial Therapy"?

Two phrases recur throughout the literature: "drugs of choice" and "appropriate therapy." The availability of many effective alternatives for most infectious syndromes renders the concept of "drugs of choice" somewhat obsolete. The second phrase—"appropriate antimicrobial therapy"—often appears in discussions, but is seldom defined. I shall attempt to provide a history of this phrase and shall then suggest alternatives.

Historical perspective. The phrase "appropriate antimicrobial therapy," as now used, seems to have first appeared in the results section of a 1968 paper by Freid and Vosti on Gram-negative bacteremia.[3] These authors based their definition on the previous observations by McCabe and Jackson that patients with Gram-negative bacteremia who had received an antibiotic to which the infecting microorganism was susceptible in vitro had lower mortality than other patients.[4] Freid and Vosti therefore defined "appropriate antibiotic therapy" as "the administration of one or more agents effective in vitro against the infecting microorganism." These and many subsequent investigators demonstrated that patients with Gram-negative bacteremia who received "appropriate antibiotic therapy" had lower mortality than patients who received "inappropriate" therapy.[5] Only occasional authors stipulated that to be "appropriate," therapy should also be prompt—for example, within the first 24 hours of onset of bacteremia.[6,7]

In 1977 Dr. Eric Brenner and I began a prospective study of all documented episodes in the four major hospitals serving a metropolitan area of 400,000 population. Interested especially in the decisions made by clinicians at the time blood cultures were obtained from patients with suspected septicemia, we considered antibiotic therapy appropriate "if an agent effective against the bacterium isolated from blood cultures had been administered in sufficient dosage and by a proper route of administration on the calendar day that the first positive blood culture was obtained."[8]

Initial analysis of our data indicated no clear-cut benefit of "appropriate" therapy as opposed to "inappropriate" therapy. Analyzing 2,978 episodes of bacteremia, we then compared the mortality among patients who received "appropriate" therapy with the mortality of patients who received three different types of "inappropriate" therapy (Table I). Mortality due to bacteremia was 15.5% for patients who received "appropriate" therapy and 14.0% for patients who received "inappropriate" therapy. Although the greatest mortality occurred in patients who received no therapy whatsoever, patients who received "appropriate" therapy had a greater mortality com-

TABLE I. OUTCOME OF 2,978 EPISODES OF BACTEREMIA AS A FUNCTION OF ANTIMICROBIAL THERAPY*

Therapy (number of episodes)	*Mortality†*	*Relative risk‡*
Appropriate§ (1,634)	15.5%	1.69 ($p<0.005$)
Inappropriate‖ (467)	14.6	1.48
Delayed¶ (675)	10.7	1.00
None** (202)	22.3	2.34 ($p<0.001$)

*For methods of data collection, see reference 8.

†Mortality attributed to bacteremia[8]

‡Relative risk of bacteremic death compared to patients who received delayed therapy

§For definition see text.

‖Administration of a drug ineffective in vitro and/or not considered to be a "drug of choice" or use of an inadequate dose or an improper route of administration on the day on which positive blood cultures were first obtained

¶Instances in which no antimicrobial agent was given on the day on which positive blood cultures were first obtained, but in which correct therapy was given subsequently

**Instances in which no antimicrobial agent was given during the week after positive blood cultures were first obtained.

pared to those who received "delayed" therapy or "incorrect" therapy at the time of antibiotic administration (Table I).

We concluded that these observations differed from those of previous investigators largely because of our definition of "appropriate antimicrobial therapy." By considering therapy as "correct" or "incorrect" both at the time blood cultures were obtained and subsequently, we reconciled our findings with those of previous authors.[9] The term "appropriate antimicrobial therapy" as used by epidemiologists may correlate poorly with clinical reality. In some instances (for example, good-risk patients without bedside evidence of "toxicity"), the truly "appropriate" clinical decision may have been to obtain blood cultures and await further developments rather than to prescribe broad-spectrum presumptive antibiotic therapy. In other instances (for example, granulocytopenic cancer patients with septic shock), use of certain drugs may be "inappropriate" despite in vitro efficacy.

More recently, the phrase "appropriate antimicrobial therapy" has been used in discussions of cost-effectiveness.[1] There may be poor correlation between what seems "appropriate" to a committee setting guidelines and what seems "appropriate" to a clinician caring for a patient.

Proposed alternatives. The term "appropriate" antimicrobial therapy may serve too many masters. I suggest different terms for different users: "effective therapy," "appropriate therapy," and "recommended therapy" (Table II).

"Effective antimicrobial therapy" would consist of the use of an agent shown to be active in vitro and/or generally regarded as a drug of choice

TABLE II. PROPOSED CATEGORIES FOR EVALUATION OF ANTIMICROBIAL THERAPY

Category	*Basis**	*Designated users*
"Effective therapy"	*In vitro* data	Epidemiologists conducting studies
"Appropriate therapy"	Above plus clinical setting	Clinicians caring for patients
"Recommended therapy"	Above plus cost factors	Policy makers seeking to contain costs

*For expanded definitions see text.

for the infecting microorganism administered in adequate dose and by a suitable route. This definition would serve the needs of epidemiologists seeking to determine the relationship between antimicrobial usage and outcome.

"Appropriate antimicrobial therapy" would consist of therapy considered optimal for a given clinical situation. This term would encompass the notion of effective therapy but would also take into account such judgmental matters as the degree of diagnostic certainty, the severity of underlying disease, and the severity of the infectious syndrome. This definition would serve the needs of physicians caring for individual patients. It might also be used by audit committees seeking, on a case-by-case basis, to monitor cost and outcome.

"Recommended antimicrobial therapy" would refer to regimens based on the deliberations of a policy-setting body such as the hospital's pharmacy and therapeutics committee. This definition would encompass not only "effective therapy" and "appropriate therapy," but would also take into account costs. This definition would serve the needs of policy makers, administrators, and medical staffs seeking to reduce the cost of medical care.

The infectious diseases physician logically assumes each of the several roles summarized in Table II. As epidemiologist and as occational clinical investigator, he applies the definition of "effective" therapy to his tabulations of local antibiotic susceptibility patterns and to his retrospective surveys of outcome. As a clinical consultant, he applies the definition of "appropriate" therapy to the care of individual patients. As a policy maker, he applies the definition of "recommended therapy" to the issue of what should represent the conventional approach to common clinical situations at his hospital. It is this last consideration that concerns us here.

Guidelines for "Recommended Antimicrobial Therapy"

There are three categories of antimicrobial therapy: preventive, presumptive, and precise.[10] Guidelines for preventive antimicrobial therapy gener-

ally apply to routine or standing orders and therefore become relatively straightforward. Guidelines for presumptive therapy are more difficult to formulate because clinical judgment regarding host factors and the severity of infection must be evaluated. Guidelines for precise therapy must address the issue of therapeutic adequacy versus overkill.

Preventive antimicrobial therapy. No attempt will be made to review the many and changing indications for perioperative prophylactic therapy.[11,12] Newer agents, usually more expensive than older ones on a gram-for-gram basis, continue to be introduced and promoted as more cost-effective for various reasons such as longer serum half-life or greater tissue penetration. Formulation of guidelines for "recommended therapy" thus is fraught with complexities. The numerous arguments for one or another regimen tempt us to ignore two lessons of history: Listerian principles are more important than prophylactic antibiotics,[13] and perioperative prophylaxis can be extremely brief without sacrificing efficacy.

The infectious diseases physician should be an impartial advocate for the most cost-effective preventive regimens. Familiar with the problems faced by his surgical colleagues and abreast of the literature, he should work closely with the medical staff to formulate optimal guidelines. The potential savings are substantial. Whether a typical orthopedic surgeon uses cefamandole or cefazolin prophylaxis for patients undergoing total hip replacement produces an added annual expense approximating $20,000 based on current average wholesale prices.[10] Ongoing analyses of this type should be applied to all indications for both surgical and medical preventive antimicrobial therapy.

Presumptive antimicrobial therapy. Although it is ideal that therapeutic (as opposed to prophylactic) use of antibiotics should be guided by knowledge of the specific infecting pathogens, this is frequently not the case in clinical practice. Prevalence surveys in American hospitals demonstrate that only 20 to 25% of all antibiotic use is based on the results of culture and sensitivity tests. This phenomenon appears to be worldwide. A study in Italian hospitals revealed that only 2% of antibiotic usage was based on the results of sensitivity tests.[14]

Several considerations justify a large portion of such widespread presumptive therapy: therapeutic urgency (as in septic shock); difficulty of obtaining specimens free of contamination for culture (as in pneumonia); and difficulty in interpretation of cultures (as in polymicrobial soft tissue infections).[15] Guidelines for presumptive therapy must address questions that often require considerable judgment: the likelihood that infection explains

TABLE III. DAILY COSTS OF SOME ANTIMICROBIAL REGIMENS FOR PRESUMPTIVE THERAPY OF SUSPECTED SEPSIS*

Regimen	*Cost ($)*
Penicillin G, 20 million units IV q24h by continuous infusion plus gentamicin, 120 mg IV q8h plus metronidazole, 750 mg orally q8h	47.95
Cefoperazone, 2 g IV q12h	53.32
Ceftriaxone, 2 g IV q24h	58.88
Cefazolin, 1 g IV q8h plus gentamicin, 120 mg IV q8h	65.71
Ceftizoxime, 2 g IV q8h	72.06
Nafcillin, 2 g IV q6h plus gentamicin, 120 mg IV q8h	90.63
Cefotaxime, 2 g IV q6h	107.46
Nafcillin, 1.5 g IV q4h plus tobramycin, 120 mg IV q8h	121.85
Cefotaxime, 2 g IV q4h	143.28
Piperacillin, 3 g IV q4h plus tobramycin, 120 mg IV q8h	143.48
Cefazolin, 1 g IV 18h plus ticarcillin, 3 g IV q4h plus gentamicin, 120 mg IV q8h	143.83
Azlocillin, 3 g IV q4h plus amikacin, 500 mg IV q8h	186.78
Cefamandole, 2 g IV q6h plus azlocillin, 3 g IV q4h plus tobramycin, 120 mg IV q8h	224.90

*Daily costs based on average wholesale prices in January 1986 and assuming administration costs of $5.00 for each intravenous (IV) infusion.[10]

the clinical findings, the most likely pathogens, the severity of the infection, and the severity of the underlying medical condition. To an increasing extent, these questions raise the issue whether older, less-expensive regimens should suffice or whether newer and much more costly antimicrobial agents offer substantial advantages.

For example, let us briefly consider presumptive therapy for suspected septicemia. Daily costs of some representative regimens shown in Table III range from $48 to $225 per day. Although one can argue that a proved and relatively inexpensive regimen such as cefazolin plus gentamicin should be standard therapy for most patients, recent observations suggest that newer alternatives may be superior. Smith et al.[16] found a high-dose cefotaxime regimen not only safer but more effective than the combination of tobramycin plus nafcillin. The differences in costs of various competing regimens are even more dramatic with certain other syndromes such as bacterial pneumonia.[10]

The infectious diseases physician should assume the leadership role in formulating guidelines for "recommended therapy" that will apply to most clinical situations. These guidelines should reflect "effective" therapy based on in vitro susceptibility data from his own institution. A high prevalence of drug-resistant bacteria such as beta-lactam-resistant *Staphylococcus aureus* or gentamicin-resistant *Klebsiella pneumoniae* may necessitate relatively expensive regimens. Outcome audits of "appropriate therapy" based on scru-

tiny of individual case records may provide valuable feedback as to the adequacy of such guidelines. Finally, the infectious disease physician may conduct clinical trials aimed at determining the most cost-effective approach to common syndromes.

Precise antimicrobial therapy. Precise therapy—that is, therapy guided by the results of culture and sensitivity results—should in theory be amenable to easily-formulated guidelines.Treatment of pneumococcal pneumonia with 600,000 units of procaine penicillin G every six hours provides optimal inexpensive therapy for all but the most complicated patients. However, even the pneumococcus has demonstrated its potential for drug resistance. The temptation to employ vast overkill in this and other documented infections is ever-present.

With knowledge of the cost of an antimicrobial agent, its predicted or measured peak serum concentration, and its minimum inhibitory concentration against an isolated microorganism, one can readily calculate "how much drug one gets for the money" or the "daily kill per dollar."[10,17] However, the necessary "kill ratio"— usually expressed as the serum bactericidal titer—remains unestablished despite years of debate. Weinstein et al. recently reported that therapeutic efficacy correlated with a peak serum bactericidal titer of 1:64 or greater or a trough titer of 1:8.[18] These values are higher than those usually recommended, and were based on only nine bacteriologic failures among 129 patients. Popularization of cost-effective methods to determine the serum bactericidal titer would facilitate the collection of data to formulate more cost-effective guidelines than exist at present.

The infectious diseases physician can formulate guidelines for his institution based not only on national guidelines and recommendations but on data from his hospital regarding both susceptibility patterns and the true cost of various antimicrobial agents.

Policies and cost containment. Cost of antibiotics can be divided into four categories: acquisition costs or the pharmacy's purchase price, administration costs (delivery systems and personnel), monitoring costs (blood tests and serum assays), and cost of consequences (adverse effects and failure to cure infection). Cost-control measures apply to each of these areas (Table IV).[10] While the issues are sometimes complex, the potential for savings are enormous.[1]

Role of the Infectious Diseases Physician

Guidelines for antimicrobial therapy in the age of cost containment inevitably pose a tension between bedside compassion and fiscal responsibility. Many people within an institution can and should contribute to the formu-

TABLE IV. PRINCIPAL DETERMINANTS OF THE COST OF ANTIMICROBIAL THERAPY AND SOME CONTROL MEASURES

Determinant	*Control measures*
Acquisition costs	Competitive bidding
	Closed formulary
	Generic substitutions
	Therapeutic equivalency substitutions
	Use of less expensive alternatives
Administration costs	Oral or intramuscular therapy when possible
	Cost-effective delivery systems
	Outpatient therapy when possible
Monitoring costs	Judicious use of serum assays and other tests
Cost of consequences	Early recognition of therapeutic failure
	Early recognition of unwanted effects

lation of such guidelines. However, the role of the infectious diseases physician should be especially pivotal. Fellowship training uniquely prepares infectious diseases physicians not only to be concerned patient advocates but to appreciate the advantages and limitations of both older and newer therapeutic strategies.

To fulfill this role, an infectious diseases physician must develop leadership and diplomatic skills. He must listen patiently to the concerns and demands of the medical staff, the administration, the pharmacy , and even pharmaceutical company representatives. He must resist the temptation to enshroud guidelines for "recommended therapy" with an aura of permanence, however difficult their formulation may have been. These guidelines should be subject to change not only on the basis of observations and opinions from afar, but on the basis of observations at his own institution. In addition to the formulation of guidelines, he should be involved in efforts both to implement and to audit the prescribing process.[1]

The problem of reimbursement. Some of our leaders argue that infectious diseases physicians should remain primarily researchers. Petersdorf[19,20] has especially taken this position, suggesting that such physicians "be based in academic divisions and devote their clinical time and effort to the care of complex referrals and indigent patients."[20]

Published demonstrations that guidelines for cost-effective antimicrobial therapy can be successfully implemented emanate almost exclusively from teaching hospitals. The authors of these demonstrations were no doubt subsidized primarily by teaching salaries or grants. In the private sector, the infectious diseases physician usually finds his expertise in such matters in

great demand—as long as there is no charge.[21,22] Appointed to pharmacy and therapeutics committees, targeted by pharmaceutical representatives, and "curbsided" by his colleagues,[23] a practicing infectious diseases physician devotes untold hours to the problem of antimicrobial use policy with no hope for reimbursement.

That medical fee schedules provide great rewards for operative procedures but little or none for valuable cognitive services is a serious aberration of our society.[24] After 13 years of post-high school preparation for a career, the infectious diseases physician may even have difficulties making ends meet unless he finds some means of subsidization.[20,21] Yet, in most communities he will be the most influential person in an enterprise worth hundreds of thousands of dollars each year. To recoup even partially the huge investment in training, an infectious diseases physician may seek income from speaking engagements sponsored by pharmaceutical firms or through ventures in which he stands to profit directly from the sale of antibiotics for outpatient therapy. The latter activity raises the specter of serious conflict of interest.[25]

Hospitals should employ infectious diseases physicians for the explicit purpose of formulating and implementing antimicrobial therapy guidelines. The savings would more than offset the salary. Influencing one surgeon to make one policy change could save $20,000 yearly. Influencing only three or four surgeons to do likewise would justify a respectable salary. Although infectious disease physicians should participate in clinical studies, they should avoid situations which would be a conflict of interest.

SUMMARY

Formulation of guidelines for antimicrobial therapy has become a dynamic process, making obsolete the old concept of relatively static "drugs of choice." Another term, "appropriate antimicrobial therapy," has been widely used by infrequently defined. Three categories are proposed: "effective therapy" (based primarily on in vitro susceptibility data); "appropriate therapy" (taking clinical judgment into account); and "recommended therapy" (taking cost into account).

Individuals with diverse backgrounds can and should contribute to the formulation of guidelines for "recommended therapy" at a given institution. However, the infectious disease physician should occupy a unique and pivotal role. Through ongoing scrutiny of the literature, dialogue with the medical staff, consultation with the pharmacy, participation in the audit process, and involvement in clinical studies, the infectious disease physician should

provide important input into all three areas of antimicrobial therapy: preventive, presumptive, and precise.

Cost-effective antimicrobial therapy, with its potential for enormous savings, cannot become a reality without ongoing formulation and implementation of effective guidelines. Hospitals should find it to be to their increasing advantage to reimburse infectious diseases physicians for this purpose. In turn, such physicians must eschew even the appearance of conflict of interest.

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